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EXAMINER	
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1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,075	MAMCHUR, STEPHEN A.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *123-184* is/are pending in the application.

4a) Of the above claim(s) *139 and 159* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *123-138,140-158 and 160-184* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/3/09 and 8/12/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 123-184 are pending in the present application. Claims 139 and 159 have been withdrawn by the applicant as being drawn to a non-elected invention. Thus, claims 123-138, 140-158 and 160-184 are examined herein on the merits for patentability.

Claim Objections

1. Claim 146 is objected to because of the following informalities: the claim does not end with a period. Each claim begins with a capital letter and ends with a period. Appropriate correction is required.

Specification

The amendments to the specification filed 15 July 2009 have been entered.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 125 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, claim 125 recites a percent of ethoxy diglycol

and propylene glycol. However, it is unclear whether the percentage of each component is percent by weight, volume, etc. For the purposes of examination, the claims are construed as percent by weight.

2. Claim 123 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "essentially free of" in claim 123 is a relative term which renders the claim indefinite. The term "essentially free of" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification teaches anhydrous compositions, but does not teach compositions "essentially free of" water.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 123, 126, 127, 132, 135, 138 and 140 are rejected under 35 U.S.C. 102(b) as being anticipated by Chiang et al. (WO 90/11064).

Chiang et al. disclose compositions comprising up to 15 wt.% drug (i.e., 5 wt.% estrogen and 10 wt.% progestrogen) and 5-40 wt.% enhancer composition (i.e., 80:20 v/v Transcutol/PGML (diethylene glycol monoethyl ether/propylene glycol monolaurate)) and up to 4 wt.% silicone oil (pg. 13, ln. 1-10). Chiang et al. further disclose that in a particularly preferred embodiment, the composition comprises one or more estrogens as well as one or more progestogens (pg. 9, ln. 7-9). Chiang et al. provide examples wherein the compositions comprise saturated estradiol in varying ratios of Transcutol and commercial propylene glycol monolaurate which comprises 5-10 wt.% propylene glycol (Example 2). Further examples comprise 5 wt.% estradiol and 14 or 20 wt.% enhancer (Transcutol/PGML) and 81 or 75 wt.% silicone oil (pg. 24, Example 6, Table 6).

Chiang et al. further disclose that the composition may in addition include one or more selected carriers or excipients, and various agents and ingredients commonly employed in dermatological ointments and lotions, such as fragrances, opacifiers, preservatives, anti-oxidants, gelling agents, perfumes, thickening agents, stabilizers, surfactants, emollients, coloring agents, and the like (pg. 11, ln. 10-17).

Thus, Chiang et al. clearly disclose compositions comprising a hormone, Transcutol and propylene glycol (obtained from the commercial PGML), wherein the compositions do not comprise water.

2. Claims 141, 147, 148, 155, 160, 161, 168, 169, 179 and 180 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosenbaum et al. (US 5,709,878).

Rosenbaum et al. disclose that dehydroepiandrosterone (DHEA) and phospholipid can be combined with little or no other material present into a concentrate suitable for facilitating the subsequent compounding of a variety of formulations presenting the composition of this invention. Even greater concentrations of DHEA can be achieved in a mixed solvent system combining phospholipid with ethyl alcohol, cetyl alcohol, and a medium chain length triglyceride. Such concentrates can conveniently include 10 to 15 parts by weight of DHEA and 85 to 90 parts of phospholipid. Presentations for use of the composition of this invention can, for example, take the form of pastes, gels, and liquids such as solutions, emulsions, creams, and lotions. In addition to DHEA compound and phospholipid, the composition of the invention can include a topically acceptable carrier and such adjuvants as are helpful for convenient dispensing and application of the composition by such presentations as pastes, gels, liquid forms such as solutions, emulsions, creams, and lotions, as well as transdermal delivery systems (col. 4, ln. 6-27). Rosenbaum et al. disclose that the phospholipid component of the composition of this invention is outstandingly effective in assisting the penetration of a DHEA compound through the skin and the establishment of increased serum concentrations of DHEA sulfate in the recipient (col. 6, ln. 56-62).

Rosenbaum et al. further provide examples wherein a concentrated premix of DHEA is prepared followed by addition of a suitable carrier and administration to an individual in the necessary dosage to treat said individual (Examples 1-25). Therefore,

Rosenbaum et al. disclose compounding the hormone DHEA in a penetration enhancing solvent for administration to patients.

3. Claims 132, 133, 135, 138, 141, 143, 146, 151, 155, 158, 160, 162-164, 167, 179 and 180 are rejected under 35 U.S.C. 102(b) as being anticipated by Carrara et al. (WO 02/11768).

Carrara et al. disclose a penetration enhancing system for transdermal or transmucosal administration of hormones comprising as a permeation enhancer fatty alcohol, propylene glycol, water and diethylene glycol monoethyl ether (Abstract; and pg. 7, ln. 13-32). Carrara et al. disclose that the preferred embodiments comprise the following actives: testosterone present at 0.05-10 wt.%, preferably 0.1-5 wt.%, more preferably 0.6-4 wt.%; estradiol present at 0.02-3 wt.%, preferably 0.04-2 wt.%, more preferably 0.06-0.12 wt.%; ethynil estradiol present at 0.02-3 wt.%, preferably 0.04-0.5 wt.%, more preferably 0.06-0.12 wt.%; levonorgestrel present at 0.02-3 wt.%, preferably 0.04-0.5 wt.%, more preferably 0.06-0.12 wt.%; and progesterone present at 0.1-10 wt.%, preferably 0.1-5 wt.%, more preferably 1-3 wt.% (pg. 11, ln. 16-32). Carrara et al. further disclose examples comprising the above actives with a fatty alcohol, propylene glycol, water and diethylene glycol monoethyl ether (Examples 1-22, 34, 35 and 40-47).

Therefore, Carrara et al. disclose a hormone composition comprising up to 3 wt.% estradiol and/or ethynil estradiol in a penetration enhancing system comprising propylene glycol and Transcutol.

4. Claims 141, 142, 151-155, 158, 160-163, 172-176, 179 and 180 are rejected under 35 U.S.C. 102(e) as being anticipated by Muni (US 6,708,822).

Muni discloses compositions and methods for the convenient compounding of pharmaceuticals wherein single and multiple unit of use kits are provided which contain all the necessary components required for preparing a compounded pharmaceutical (Abstract). Muni states that compounding of pharmaceuticals in its broadest sense refers to the preparation, mixing, assembling, packaging and/or labeling of a drug or device usually resulting from a prescription order from a physician. Under current Food and Drug Administration (FDA) regulations, a qualified pharmacist or a qualified physician can compound a valid prescription for medical or therapeutic use provided the prescription is unsolicited, the pharmacist or physician compounds only one prescription at a time, the patient for whom the prescription is meant is identified, and only FDA acceptable components are used to fill the prescription (col. 1, ln. 16-28).

Muni discloses that there exists a need for a convenient method for preparing accurate and efficacious compounded pharmaceutical formulations. Such a method would undoubtedly be amenable to most pharmacists, resulting in an increased availability of compounded pharmaceuticals to patients. The invention provides compositions for the preparation of compounded pharmaceuticals, as well as methods for their use. In particular, in one aspect, the invention provides a kit comprising the pharmaceutical and handling elements required for producing a compounded pharmaceutical formulation. The kits of the invention contain pre-measured amounts of

active and inactive (e.g., base) agents for the preparation and filling of single or multiple prescriptions, and are thus referred to as `unit-of-use` kits (col. 2, ln. 21-36).

Muni discloses that the invention aims to facilitate the compounding of pharmaceuticals by most pharmacies by providing kits which contain all the necessary components and equipment necessary to prepare with ease a unit of use dose. A unit of use kit would contain a pre-measured amount of each component sufficient to prepare enough of a compounded pharmaceutical to last for a period of time, as specified by the prescribing physician (col. 6, ln. 1-23).

Muni discloses that the active and inactive agents are physically mixed by a pharmacist to produce a compounded pharmaceutical composition. In other embodiments, the inactive agents are pre-mixed with the active agents and it is the mixture of the active agents which constitutes a compounded pharmaceutical. It is intended that the compounded compositions and the compounding methods of the invention be performed by either a qualified pharmacist or a qualified physician (col. 2, ln. 66 to col. 3, ln. 7).

Muni discloses in one embodiment, the first and second containers and the instructions may be housed in a package. In another embodiment, the kit contains a mixing element. The first container may also contain an inactive agent selected from the group consisting of a suspending agent and an anti-foaming agent. Preferably, the inactive agent in the first container is not a base inactive agent. The second container preferably contains an inactive agent selected from the group consisting of a base such as a gel or a lotion, a cream, or an ointment, and a liquid base. In some embodiments,

the second container also contains a suspending agent, an anti-foaming agent, or both. In yet another embodiment, the at least one inactive agent is a suspending agent. Preferably the suspending agent is propylene glycol (col. 3, ln. 10-28).

Muni discloses the kit may contain three or more active agents. The active agents may be estrone, estradiol and progesterone, or estriol, estrone, estradiol and progesterone. In variations, the progesterone may also be omitted such that the kits comprise estrogens alone as active agents (col. 3, ln. 47-55). In another embodiment, the invention provides a kit for compounding pharmaceuticals comprising a plurality of containers each housing an active agent pre-mixed with at least one inactive agent and instructions for use. Some such kits may also include a package into which the plurality of containers and the instructions are housed. Each active agent is pre-measured into a respective unit of use amount. The mixture of the active agents is a compounded pharmaceutical (col. 3, ln. 64 to col. 4, ln. 5).

Muni discloses that an important class of compounded pharmaceuticals intended to be provided by the kits of the invention is that used in hormone replacement therapy (HRT). There are many types and forms of hormone replacement therapy available to aging women. Typically, these compounded formulations comprise a combination of one or more estrogens and one progesterone. The importance of individualized therapy and the physician-pharmacist-patient relationship in providing optimal HRT is well documented. Rather than prescribing a very limited number of FDA approved HRT products, physicians are choosing and selecting various natural hormone combinations for post-menopausal women. Based upon family history and present health of a patient,

a 30 day supply of Triest (i.e., three estrogen combination) or Biest (i.e., two estrogen combination) regimen with or without progesterone is commonly prescribed. Triest includes a mixture of estriol, estradiol, and estrone while Biest contains estriol and estradiol. Pre-weighed mixtures of these natural hormones which are all commercially available and FDA accepted, along with pre-weighed diluent (e.g., lactose) would easily be supplied in a typical 30-day unit of use kit (col. 7, ln. 1-20). Example 2 of Muni discloses compounding a solution of testosterone and Example 7 discloses compounding an 8:1:1 ratio of estriol, estrone and estradiol. Also see claims 1, 2, 6-9, 18, 19, 28, 30-39, 41 and 42.

As can be clearly seen, Muni discloses compounding hormones for hormone replacement therapy wherein the pharmacist compounds the necessary ingredients according to a prescription by a doctor for individualized patient treatment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 123-138, 140-158 and 160-184 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muni (US 6,708,822) in view of Chiang (WO 90/11064), Carrara et al. (WO 02/11768) and Gallili et al. (US 6,541,001).

Determination of the scope and content of the prior art

(MPEP 2141.01)

The teachings of Muni are discussed above and incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Muni does not teach the estrogen concentration dissolved in a solvent or wetting agent, as instantly claimed. However, Muni does teach a ratio of 8:1:1 of estriol, estrone and estradiol in a compounded composition. Also, Chiang teaches skin permeation enhancer compositions for transdermal administration of steroidal hormones wherein a composition comprises 5 wt.% estradiol and 14 or 20 wt.% enhancer (Example 6). Also, Carrara et al. teach transdermal administration of hormones and penetration enhancers wherein the hormone is: testosterone present at 0.05-10 wt.%, preferably 0.1-5 wt.%, more preferably 0.6-4 wt.%; estradiol present at 0.02-3 wt.%, preferably 0.04-2 wt.%, more preferably 0.06-0.12 wt.%; ethynil estradiol present at 0.02-3 wt.%, preferably 0.04-0.5 wt.%, more preferably 0.06-0.12 wt.%; levonorgestrel present at 0.02-3 wt.%, preferably 0.04-0.5 wt.%, more preferably 0.06-0.12 wt.%;

and/or progesterone present at 0.1-10 wt.%, preferably 0.1-5 wt.%, more preferably 1-3 wt.%; and the penetration enhancers comprise a fatty alcohol and diethylene glycol monoethyl ether in combination with a ternary vehicle comprising propylene glycol, alcohol and water (pg. 11, ln. 16-32).

Muni also does not teach the compounded pharmaceuticals comprising diethylene glycol monoethyl ether and propylene glycol as the penetration enhancers without water, as instantly claimed. However, Carrara et al. teach hormone compositions suitable for transdermal administration comprising fatty alcohol, propylene glycol, water and diethylene glycol monoethyl ether (pg. 7, ln. 13-32). Muni teaches that the inactive agents can function in many other ways such as to provide a base in which the active agent can be dissolved or suspended, to dilute the active agent in order to provide proper doses upon administration, to facilitate the dissolution or suspension of the active agent, or to prevent oxidation of the active agent by removing air bubbles from the final compounded suspension (col. 8, ln. 25-53). Muni further teaches that the active and the base may be packaged separately (col. 12, ln. 45-65). Therefore, it would have been prima facie obvious to provide the active hormone in a container separate from the water.

Muni also does not teach the compounded pharmaceutical preparation comprising colorants or dyes for identification purposes, as instantly claimed. However, it is well-known that steps to prevent or reduce errors in administrating incorrect prescription medication are desired. For instance, Gallili et al. disclose color-coding different vaccines with a dye to ensure against mistakenly administering the incorrect

vaccine (col. 21, ln. 15-26). Therefore, it would have been prima facie obvious to incorporate dyes or coloring agents into the compounded compositions of Muni in order to ensure against mistakenly administering the incorrect medication.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to compound hormone compositions comprising estrogens, penetration enhancers, and coloring agents for identifying the different hormone compositions.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616